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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,845	03/14/2000	REINER LAUS	7636-0013.10	6520

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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	13

DATE MAILED: 06/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/402,845	Laus et al
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 7, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above, claim(s) *5-9 and 14-22* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4 and 10-13* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Election filed May 7, 2002 (Paper No. 12) in response to the Office Action of March 26, 2002 (Paper No. 11) is acknowledged and has been entered. Claims 1-22 are pending in the application and Claims 5-9 and 15-22 have been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-4 and 10-13 are currently under prosecution.

2. Applicant's election with traverse of Group I, claims 1-4 in Paper No 12 is acknowledged. Applicant admits on the record that the inventions of Groups III and IV are independent or distinct from Group I, however the traversal is on the ground(s) that the search of the inventions would not impose a serious burden on the examiner. This is not found persuasive for the reasons set forth in Paper No. 11 and further because the literature search, particularly relevant in this art, is not coextensive. Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Objections to the Specification

3. The specification on page 2 of the claims is objected to because it appears that claim 11 has been deleted, but that a phrase "[human prostatic acid phosphatase (PAP)] has been left on the page. The phrase is not associated with any claim and it is not clear what it is doing there. A review of claim 10 reveals that the claim ends with a period (.) And therefore the phrase is not associated with claim 10. A review of claim 12, apparently amended to be claim 11, reveals that the claim starts with a

capitol letter. And therefore the phrase is not associated with claim 11 (formerly claim 12). Appropriate correction is required.

4. The specification on page 2, lines 28-29 recites the phase "PAP antigen can be formed with by substituting into the polypeptide sequence". There appears to be an inadvertent typographical error. Examiner has made an attempt to identify such informalities but Applicant must review the specification and point out and correct any additional informalities of this type. Appropriate correction is required.

5. The specification on page 1 should be amended to reflect the status of the parent applications. For example,

"This application is a 35 USC 371 application which claims benefit of provisional application number 60*********, filed ********, now abandoned."

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

7. Claims 1-3 and 12-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:2 and therefore the written

description is not commensurate in scope with the claims drawn to mouse PAP (which reads on all forms of PAP in mouse), isolated polypeptides comprising sequences having at least 90% identity, 95% identity to SEQ ID NO:2, polypeptides comprising amino acid sequences of SEQ ID NO:2 including conservative amino acid substitutions thereto, wherein said substitutions do not alter said sequence by more than about 10%. The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

The specification discloses an isolated SEQ ID NO:2. The claims, as written, however, encompass polypeptides which vary substantially in composition. Further, the instant disclosure of a single species of polypeptide does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera. A description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by amino acid sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description, of the sites at which variability may be tolerated

and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed and no identifying characteristic or property of the instant polypeptides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of a specific polypeptide sequence is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

8. Claims 1-3, 12 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide comprising SEQ ID NO:2, does not reasonably provide enablement for polypeptides comprising sequences having at least 90% identity, 95% identity to SEQ ID NO:2, polypeptides comprising amino acid sequences of SEQ ID NO:2 including conservative amino acid substitutions thereto, wherein said substitutions do not alter said sequence by more than about 10%. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The claims are drawn to polypeptides attached to SEQ ID NO:2. This includes polypeptides with chemical modifications, deletions, truncations, substitutions and conjugations. However, Applicant has not shown that polypeptides with these types of differences from SEQ ID NO:2 are capable of functioning as that which is being disclosed. Applicant has not enabled all of these types of modified polypeptides because it is well known in the art that the effects, on the functionality of a polypeptide, of altering even one amino acid cannot be predicted. For example, Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led

to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly with up to 10% difference between SEQ ID NO:2 and the claimed polypeptides it could not be predicted, nor would it be expected that the function and activity of the claimed polypeptides would be the same as that of SEQ ID NO:2. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is

enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with up to a 10% dissimilarity to SEQ ID NO:2, the function of the claimed polypeptides could not be predicted, based on sequence similarity with SEQ ID NO:2, nor would it be expected to be the same as that of SEQ ID NO:2.

9. Claims 10-13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10-13 are indefinite in the recitation of "a method of inducing an immune response against [-] in a mammalian subject". The claims are indefinite

because the preamble of the claim does not state an antigen against which an immune response is raised.

Claim 12 is indefinite in the recitation of "wherein said mouse PAP is selected according to any of claims 1-4". The claims are indefinite because claims 1-4 are not method claims and it is not clear how selection can be made according to any of claims 1-4. The rejection can be obviated by amending the claims to recite, for example, wherein said mouse PAP is selected from the group including the polypeptides recited in any of claims 1-4.

Claim 13 is indefinite in the recitation of "said xenogeneic antigen". There is no antecedent basis for the limitation in the claims from which claim 13 depends.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-4 are rejected under 35 USC 102(b) as being anticipated by Iype et al (Arch. Biochem. Biophys, 1968, 128(2):434-441.

The claims are drawn to an isolated polypeptide comprising a sequence having at least 90% identity to SEQ ID NO:2, 95% identity to SEQ ID NO:2, 10% conservative substitutions of SEQ ID NO:2, having SEQ ID NO:2. The

specification teaches that SEQ ID NO:2 is a prostatic acid phosphatase isolated from mouse.

Iype et al teach a prostatic acid phosphatase isolated from mouse (see abstract). The claimed mouse prostatic acid phosphatase appear to be the same as the prior art prostatic acid phosphatase, absent a showing of unobvious differences. The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed prostatic acid phosphatase is functionally different than that taught by the prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

12. Claim 10 is rejected under 35 U.S.C. § 102(b) as being anticipated by Kuciel et al (Biotechnol. Appl. Biochem., 1988, 10(3):257-272.

Because of the indefinite nature of the claims, it is assumed for examination purposes that the preamble of the claim is meant to read "A method of inducing an immune response against a human prostatic acid phosphatase".

The claim is drawn to a method of inducing an immune response against human PAP in a mammalian subject comprising administering to the subject an immunogenic dose of a composition comprising an xenogeneic form of PAP from a different mammalian species.

Kuciel et al teach a method of inducing an immune response against human PAP by immunizing mice with human PAP which is a xenogeneic form of PAP to the mouse and wherein the human PAP is from a different mammalian species.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

14. Claims 10 rejected under 35 U.S.C. § 103 as being unpatentable over Iype et al, *Supra*, in view of Johnstone et al (Immunochemistry in Practice, 1987, 2nd Ed., Blackwell Scientific Publications, Oxford, England, pg 30).

Due to the indefinite nature of the claims, it is assumed for examination purposes that the preamble of the claim is meant to read "A method of inducing an immune response against a mouse prostatic acid phosphatase"

Iype et al teach as set forth above but do not specifically teach inducing an antibody in a mammal of a different species.

Johnstone et al teach conventional antibody production in a goat (p. 30).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to induce an immune response, which reads on producing an antibody, to the mouse prostatic acid phosphatase of Iype because the Board of Patent Appeals and interferences has taken the position that once an antigen has been isolated, the manufacture of antibodies against it is *prima facie* obvious. See Ex parte Ehrlich, 3 USPQ 2d 1011 (PTO Bd. Pat. APP. & Int. 1987), Ex parte Sugimoto, 14 USPQ 2d 1312 (PTO Bd. Pat. APp. & Int. 1990). Further, it would have been *prima facie* obvious and one of ordinary skill in the art would have been motivated to induce the immune response in a mammal to which the mouse prostatic acid phosphatase is xenogeneic because Johnstone et al teach that antibody production in a goat is conventional and one would have a reasonable expectation of success in producing said immune/antibody response.

15. No claims allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
June 6, 2002